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CASE REPORT

# Hepatocellular Carcinoma Associated with Adult-Type Citrullinemia

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KEY WORDS: adult-type citrullinemia; hepatocellular carcinoma; carcinogenesis; liver cirrhosis.

Hypercitrullinemia is a rare hereditary metabolic disorder caused by the deficiency in the activity of argininosuccinate synthetase. McMurrey et al first reported this disease in infants (1) and Saheki et al classified three types on the basis of qualitative and quantitative analysis of argininosuccinate synthetase (2). The classic neonatal and infantile forms were assigned to type I (abnormal kinetics of the enzyme) and III (undetectable or extremely low levels of the enzyme). Biochemically, the defect of the enzyme in the classical types is found in all tissues and/or cells where argininosuccinate synthetase is expressed (3). Analysis of the amplified cDNA from 14 neonatal/infantile type III citrullinemia patients identified mutations in the mRNA that are heterogeneous (4). Type II citrullinemia is an adult-onset type and is clinically characterized by a sudden onset of consciousness disturbance, a high serum citrulline concentration, and hyperammonemia. Most of this type of citrullinemia occurs in Japan unlike in the United States and Europe. Type II citrullinemia is characterized by a quantitative decrease of argininosuccinate synthetase only in the liver, while argininosuccinate synthetase levels in other tissues, such as kidney, brain, and fibroblasts, are normal. The hepatic content of the enzyme is about 10% of control value, but the translatable mRNA level for the enzyme is similar to the control value and there is no mutation in the argininosuccinate synthetase mRNA. Thus, it is confirmed that the liver contained the normal amount of mRNA coding for argininosuccinate synthetase, but there was increased degradation of the enzyme or inhibited translation (5–8).

Although there are reports of the patients of type II citrullinemia complicated by hepatocellular carcinoma, the details were not well elucidated (7, 9). Here, we report on a patient with adult type citrullinemia who developed hepatocellular carcinoma after 29 years of follow-up, and we analyzed argininosuccinate synthetase in hepatocellular carcinoma tissues.

## CASE REPORT

The patient was a 43-year-old Japanese woman with an unremarkable family history. She had a noticeable craving for nuts, beans, and meats during her childhood. The past medical history of the patient included hyperthyroidism at the age of 16. She had no history of alcohol abuse.

She was diagnosed with pancytopenia and liver dysfunction at the age of 14. Histology of her liver biopsy specimen at that time showed moderate steatosis without inflammation or fibrosis. At the age of 22, she had started to have repetitive transient and frequent disturbance of consciousness, bilateral arm choreic movements and convulsion. She was then admitted to the hospital.

Studies in the hospital revealed high plasma ammonia and a plasma aminogram that showed citrulline of 412.6 nmol/ml (normal, 17–43 nmol/ml) and arginine of 278.5 nmol/ml (normal, 54–130 nmol/ml). Serum hepatitis B surface antigen and antibodies were negative. An electroencephalogram showed triphasic waves in all regions while she was unconscious, and these waves resolved spontaneously when she regained consciousness. Celiac angiography was negative for a portosystemic shunt. Her liver biopsy showed micronodular cirrhosis with severe steatosis. She was diagnosed with adult-type citrullinemia. During her hospitalization, her protein intake was restricted to 40 g/day (1600 kcal) and lactulose was administered at a dose of 18 g/day. There was remarkable improvement of encephalopathy and lowering of her serum citrulline level to 131 nmol/ml and arginine level to 73 nmol/ml. After discharge she remained

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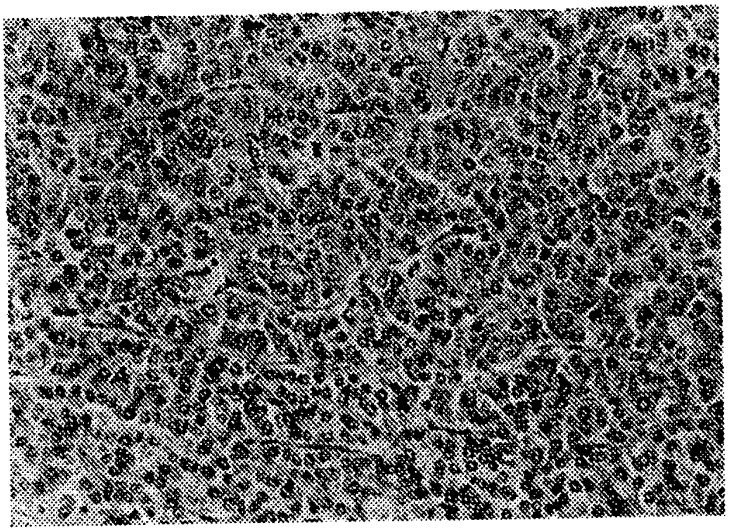

Fig 1. Pathological finding of tumor revealed moderately differentiated hepatocellular carcinoma (magnification: ×200).

in stable condition with the protein restriction and lactulose intake.

Twenty-one years later at the age of 43, the patient was admitted to the hospital because liver function studies were abnormal and an abdominal CT showed a solid mass, 20 mm in diameter with enhancement in the left lobe of the liver. On admission her obesity index was −5% according to the modification of Broca's method [0.9 × (height in cm − 100) kg]. Her plasma ammonia level was 43 μg/dl (normal, 33 ± 15 μg/dl). Results of liver function tests were abnormal: aspartate aminotransferase (AST) concentration was 47 units/liter (normal, 0–30 units/liter); alanine aminotransnsferase (ALT) was 73 units/liter (normal, 0–30 units/liter). The concentrations of total protein and albumin were 7.6 g/dl (normal, 6.0–8.0 g/dl) and 4.7 g/dl (normal, 3.5–6.0 g/dl), respectively. Results of serological tests for hepatitis B and C viruses were negative. A plasma aminogram showed that citrulline and arginine concentrations were within the normal value. Serum α-fetoprotein and des-γ-carboxy prothrombin were within the normal range.

Celiac angiography disclosed a small hypervascular lesion in the left lobe without vascular invasion of either portal or hepatic vein branches. From the above findings, the tumor was suspected to be hepatocellular carcinoma, and left hepatic lobectomy was carried out. A solitary tumor nodule with a maximum diameter of 2 cm was observed along the left margin of posterior segment of the left lobe. The histological examination of the tumor revealed moderately differentiated hepatocellular carcinoma (Figure 1), and was surrounded by a fibrous capsule without tumor invasion and vascular invasion. There was a satellite nodule beside the tumor. Nontumor sites showed micronodular thin septal cirrhosis (Figure 2). The quantitative enzyme activity of both tumor and nontumor tissue were less than 10% of normal (Table 1). There were no complications or recurrence of hepatocellular carcinoma after discharge from the hospital.

## DISCUSSION

Hepatocellular carcinoma associated with type I or III citrullinemia has not been reported in United States or Europe. On the other hand, Nakaymura et al (10) pointed out the high incidence of hepatocellular carcinoma in type II citrullinemia in Japan. However, the patient's background and characteristics with hepatocellular carcinoma in adult type citrullinemia had not been well documented. Furthermore, the mechanism of heheptocarcinogenesis has not been elucidated.

Many cases of adult-type citrullinemia accompany fatty liver (11–13). In adult-type citrullinemia, ketogenesis is impaired and decreased removal of hepatic triglycerides as very-low-density lipoprotein particles causes accumulation of triglycerides (14). Persistent steatosis may progress to cirrhosis, but nonalcoholic steatohepatitis does not give rise to hepatocellular carcinoma at high incidence (15). In this case liver cirrhosis with severe steatosis was observed at the age of 23, and there is no hepatocyte injury, necrosis, or inflammatory infiltration within the background of steatosis. These findings suggested the host's immunological reaction was not involved and viral hepatitis other than HBV and HCV could be excluded in this patient.

On the other hand we may speculate that citrulline itself had promoted carcinogenesis. Excessive citrulline promotes the uptake of [6-$^3$H]thymidine in hepatocytes while other amino acids inhibit it (10). This

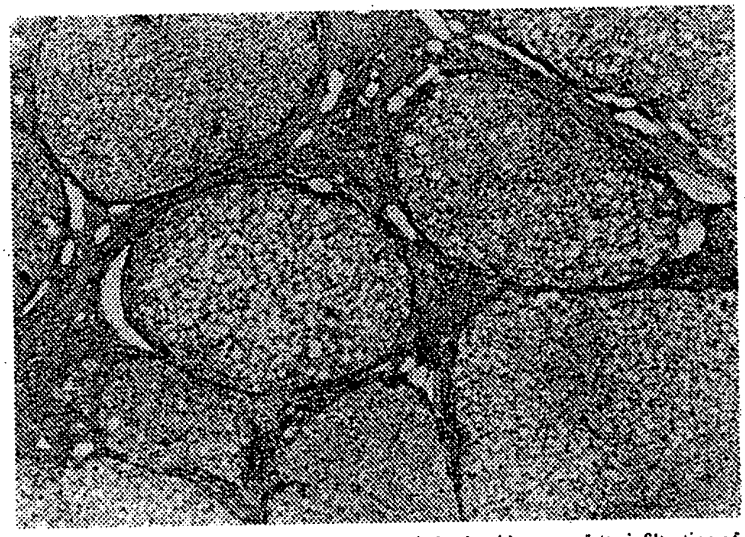

**Fig 2.** Nontumor site illustrates micronodular cirrhosis with severe fatty infiltration of the lobules without hepatocyte injury necrosis and inflammatory infiltration. (magnification: ×40).

indicates that citrulline promotes the hepatocyte proliferation and that excessive enhancement of DNA synthesis by polyamine may be a carcinogenetic promoter. Therefore, we speculated that exposure to citrulline might be enough to be hepatocarcinogenesis in this patient.

Activities of most urea cycle enzymes are decreased in both tumor and nontumor tissue, but only argininosuccinate synthetase activity in tumor tissue decreased significantly (by 90%) compared with those nontumor tissue in this patient. These data were compatible with those in adult citrullinemia with cirrhosis, since liver dysfunction impairs the urea cycle enzymes. There are two types of argininosuccinate synthetase distribution in the liver of adult-type citrullinemia; one has a homogeneous distribution and the other is clustered, as shown by an immunohistochemical method. The clustered type has a less favorable prognosis than that of the homogeneous type, and the clustered type does not develop from the homogeneous type (16, 17). Unfortunately we could not analyze these argininosuccinate synthetase distribution patterns in this patient. However, these two types may reflect different causes of citrullinemia, as well as different tendencies to cause hepatocellular carcinoma. Other genetic abnormalities for carcinogenesis related to this hereditary disorder cannot be completely excluded in adult type citrullinemia.

In considering therapy of adult type citrullinemia, we should consider the possibility of liver transplantation because the defect of argininosuccinate synthetase disorders occurs only in the liver. Liver transplantation is now a standard therapeutic approach for urea cycle disorders. Several patients with urea cycle disorders, including two patients with type II citrullinemia, underwent liver transplantation and had good postoperative courses (18–21). Liver transplantation at the early stage of adult type citrullinemia will

TABLE 1. ACTIVITIES OF UREA CYCLE ENZYMES IN LIVER*

| | *Tumor* | *Nontumor* | *Control* |
|---|---|---|---|
| Carbamylphosphate synthetase (CPS) | | | |
| units/g liver | 1.0 | 1.3 | 4.2 ± 1.3 |
| units/mg protein | 0.017 | 0.029 | 0.036 ± 0.013 |
| Ornithine transcarbamylase (OTC) | | | |
| units/g liver | 54 | 93 | 106 ± 37 |
| units/mg protein | 0.92 | 2.07 | 0.88 ± 0.35 |
| Argininosuccinate synthetase (ASS) | | | |
| units/g liver | 0.27 | 0.20 | 2.59 ± 1.13 |
| units/mg protein | 0.0060 | 0.0051 | 0.033 ± 0.012 |
| Argininosuccinate lyase (ASL) | | | |
| units/g liver | 3.42 | 1.47 | 3.42 ± 1.75 |
| units/mg protein | 0.076 | 0.038 | 0.052 ± 0.025 |
| Arginase (ARG) | | | |
| units/g liver | 221 | 397 | 1180 ± 270 |
| units/mg protein | 4.9 | 10.2 | 15.8 ± 3.1 |

* The activities of the five urea cycle enzymes in the liver were measured at the Department of Biochemistry of Kagoshima University, Japan. The results of control are expressed as mean ± SD with the number of control samples in parenthesis.

improve citrullinemia, symptoms, and finally prevent the occurrence of hepatocellular carcinoma.

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